

NEW TECHNIQUES FOR DATA FUSION IN MULTIMODAL FMT-CT IMAGING

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ABSTRACT

We examine approaches to the incorporation of anatomic structural information into the inverse problem of fluorescence molecular tomography (FMT). Using an appropriate relationship between anatomic and reconstruction image resolution, we build an inverse problem parameterized along the anatomical segmentation. These values serve as the basis for two new regularization techniques. The first regularizes individual voxels in proportion to the importance of the underlying segments in reducing the residual error. The second is based on a well known statistical interpretation of Tikhonov-type regularization in which the statistical prior is defined implicitly as the solution to a PDE whose structure is based on the anatomical segmentation. Results are shown using both techniques for a simulated experiment within the chest cavity of a mouse.

Index Terms— Inverse Problems, Fluorescence, Optical Tomography

1. INTRODUCTION

In recent years, in-vivo tomographic imaging of fluorescent probes has been the subject of significant research [1]. Using a wide range of highly specific targeted probes, fluorescence molecular tomography (FMT) has enabled in-vivo study of functional activity and important molecular biomarkers. In addition, the ability to generate three dimensional maps of fluorochrome concentration gives FMT a distinct advantage over more widely available planar techniques. Rather than simply displaying raw or processed CCD images, FMT uses physical models of light propagation in tissue to internally localize and quantify fluorochrome concentrations with a higher degree of accuracy. Recent advances in instrumentation have led to non-contact CCD based imaging techniques capable of multi-angle data collection in a free space geometry [2]. By collecting data from multiple projections, these systems are able to offer an improved resolving capability as compared to existing single projection systems.

Regardless of improvements in system design, FMT, as with all imaging techniques based on the collection of diffuse light, suffers from a low spatial resolution. This is not a defect in the imaging systems themselves but rather a result

inherent in the underlying diffusion physics. To help compensate for this low resolution, it has been suggested that a priori structural information be incorporated into the image formation process [3, 4]. This anatomical information, available from imaging modalities such as X-ray CT or MRI, is then used both in computing more accurate diffusion models and in constructing an appropriate regularization term for the fluorescence tomography problem. With the expected arrival of dual-modality imaging systems, corresponding advances in data processing and inversion techniques are needed to make optimal use of this improved data.

Existing computational methods for multi-modal data frequently label reconstruction voxels according to tissue type, and use this information to construct relationships among voxels within each tissue [3, 4]. Traits such as mean value and smoothness can then be controlled on a tissue by tissue basis, which leads to increased precision in the final reconstructions. There are, however, two issues for which these methods do not typically account. The first is that structural information is usually available at a much higher resolution than is used for the inversion of diffusion data. Particularly along boundaries, each individual voxel at the FMT scale potentially intersects two or more regions at the structural scale. In the reconstruction, errors near internal tissue boundaries could result from incorrect labeling of those voxels. Second, by establishing relationships only within each individual region these methods assume that the assigned segmentation is absolute truth, and that voxels in neighboring regions are unrelated to one another. While improvements in dual-mode data collection systems will reduce segmentation error, the assumption of isolated physical regions can easily be violated when imaging fluorescence. Taking place on the molecular level, this activity is not necessarily constrained by large scale physical anatomy. For certain applications, such as studying the spread and development of tumors, the features of greatest interest may in fact be the locations in which the fluorochrome distribution deviates from the anatomical structure, acting as an early indicator of future growth.

This paper presents two new methods to incorporate structural anatomic information into the FMT reconstruction

process which address the issues outlined above. Both approaches make use of a linear operator which establishes an appropriate relationship between voxels in the high resolution structural image and voxels in the lower resolution FMT solution space. An initial parameterized solution is then obtained to recover a single reconstruction value for each anatomical region. Our first method uses this information to construct a spatially varying regularization term which penalizes each voxel individually based on its association with the underlying anatomical regions. By regularizing regions of lower importance more heavily than those of greater importance, we are able to compute images which more accurately reflect ground truth.

Our second method looks at a classical statistical interpretation of the regularized least squares problem. It is well known that Tikhonov regularization with a smoothness penalty is equivalent to a maximum a posteriori estimation method in which the prior model is assumed to be Brownian motion, that is, a white noise driven diffusion process. We introduce a modified form of the diffusion equation which encodes the segmentation information as regions connected by specified boundary conditions. The regularization functional (equivalently, the covariance matrix of the modified diffusion process) then provides a penalty to the inverse problem in which edge information is treated in a more "relaxed" manner than is typically the case. The goal is to avoid the need to make hard decisions about voxel membership when segmentation results may not be correct. In addition to providing a new technique for analysis and interpretation of regularization operators, this method allows for the potential incorporation of complex regularization structures which would not otherwise be intuitively evident. We demonstrate both methods through their application to the inversion of data simulating the detection of fluorochrome within the murine chest cavity.

2. METHODOLOGY

2.1. Problem Definition

For source-detector separations of more than a few millimeters, the propagation of photons within tissue can be modeled using the diffusion approximation [5]. Green's functions solutions to this equation are available in closed form for simple geometries, and via numerical approaches such as the finite element method (FEM) for more complex systems. For fluorescence imaging, use of the normalized Born ratio, which normalizes received fluorescence measurements by their corresponding excitation measurements, in conjunction with the first order Born approximation, allows for a single linear system to relate the normalized data signal to the underlying physical distribution of fluorochrome [6]:

$$b = Ax + n. \quad (1)$$

Here b is the collected data A is the linearized forward operator, n is measurement noise, and x is the vector of fluorescence concentrations to be recovered. The inverse problem,

that of using b to recover the value of x , is typically solved as a regularized least squares problem:

$$\hat{x} = \arg \min_x \|Ax - b\|_2^2 + \lambda \|L(x - \mu)\|_2^2 \quad (2)$$

for some regularization matrix L and a vector of mean values μ . The regularization parameter λ is then selected for each individual data set using techniques such as the L-Curve. While the regularization matrix can be as simple as the identity, more complex matrices can impose prior knowledge about the structure of the solution.

2.2. FMT-CT Image Relationships

As previously stated, structural information available from CT images is typically of a higher physical resolution than is possible with FMT systems. Because of this, each voxel in the FMT reconstruction space will occupy the same space as several voxels in the anatomical segmentation. Attempting to simply label each FMT voxel with a single tissue type is liable to lead to labeling errors that will then be reflected in the resulting reconstruction.

A more appropriate model is to assume the existence of a solution x_{ct} , which is a map of the fluorescence distribution at the same resolution as the CT image. A matrix, denoted here as C_1^2 , can then be constructed which maps full or fractional voxels at the CT image scale (Resolution 1) to voxels at the FMT image scale (Resolution 2). Elements of C_1^2 are computed as:

$$(C_1^2)_{i,j} = \frac{v_{j \in i}}{v_i} \quad (3)$$

with $v_{j \in i}$ being the volume of CT voxel j that lies within FMT voxel i , and v_i being the total volume of that FMT voxel. This matrix will be used in both the techniques which follow.

2.3. Spatially Varying Regularization

Our initial method for using structural information is to build a regularization functional which penalizes individual voxels based on their segmentation membership. We first construct a reduced dimensional problem parameterized along the boundaries of the anatomical segmentation. The assumption is that the solution to this problem will provide information regarding which physical regions are most likely to contain fluorescence. Regions of low fluorescence probability are then penalized more than regions of high probability, to damp out unwanted artifacts and encourage solution values to be localized within the appropriate regions.

To implement this idea, we built an inverse problem based on the previously described matrix relating CT and FMT image scales. To obtain a single value for each segment, we introduce an additional matrix C_0^1 , which maps the values associated with each region onto the appropriate CT image voxels. Thus, the matrix $C_0^2 = C_1^2 C_0^1$ will map these values onto the FMT image space. This assumes a spatially constant model for the fluorescence within each region, with the columns of C_0^2 being indicator functions for the different segments, and

μ being the vector of mean values. We then construct a least squares inverse problem as:

$$\hat{\mu} = \arg \min_{\mu} \|b - AC_0^2 \mu\|_2^2 \quad (4)$$

and solve it using a non-negatively constrained steepest descent algorithm [7].

As a measure of the relative importance of each region, we compute the reduction in residual error induced by each of the individual segmented regions:

$$e_j = \|b - (AC_0^2)_{*j} \mu_j\|_2^2 \quad (5)$$

where $(AC_0^2)_{*j}$ is column j of the matrix (AC_0^2) . In order to make these terms consistent across data sets, they are normalized to generate the values $\gamma_j = e_j / \max(e_j | \forall j)$. Construction of a spatially varying diagonal regularization matrix proceeds as:

$$L = \text{diag}(C_0^2 [\gamma_1 \gamma_2 \dots \gamma_N]^T) \quad (6)$$

This matrix is used in conjunction with a mean vector set to zero to solve (2) and obtain the final reconstructed image.

Figure 1 shows an example of this method being applied to the problem of localizing lung inflammation within the murine chest cavity. Simulated data was generated on a real animal geometry using the image shown in Fig. 1a, to which 10% shot noise was added. A reconstruction regularized with the identity matrix is shown in Fig. 1b. Fig. 1d shows a reconstruction using the new method, with which the shape of the resolved anomaly is resolved more accurately, and the absolute error in the image is reduced by 6% compared to the identity matrix regularization. Compared to the reconstruction with a LaPlacian regularizer as shown in 1c, this technique has a 2% increase in error, but provides a superior match to the structure of the image. Regularization parameters were selected to minimize the absolute image error.

2.4. Differential Equations as Regularizers

A well known interpretation of Eq (2) is as a maximum a posteriori solution assuming that the image x is Gaussian distributed with mean vector μ and covariance matrix $(\lambda^2 L^T L)^{-1}$. Typically however, the construction of L does not take this directly into account, and μ is left as a vector of zeroes. L is then built to explicitly minimize image traits such as the local gradient or Laplacian. While this can quickly encode simple image constraints, more complex relationships are possible for which the appropriate regularization structure may not be readily evident.

To help enable more complex regularization for diffusion and other inverse problems with prior structural segmentations, we propose an alternative method for the generation and analysis of covariance (regularization) matrices. Rather than explicitly construct the regularization matrix, we allow it to arise implicitly from the construction of a differential equation governing the behavior of the solution image. Specifically, a stochastically driven, anatomically based differential

equation is considered. Parameters for the equation are obtained using the low dimensional inverse solution described above. To incorporate relationships between anatomical regions, boundary conditions are established for each set of neighboring regions. From this, a discretized version of the equation can be written as a linear system, which is then inverted to obtain an expression for the image in terms of the discretized differential operator and the driving noise process.

As an initial example with the potential for wide applicability, we assume that within each anatomical region Ω_m the solution $x(r)$ should obey the differential equation:

$$\alpha(\Omega_m) \nabla^2 x(r) = w_m(r) \quad (7)$$

where $\alpha(\Omega_m)$ is a smoothness constraint on each region, and $w_m \sim N(0, \sigma_m^2 I)$ is a zero mean Gaussian white noise process with variance σ_m^2 . At the boundary of each region, we impose the constraint:

$$\beta(\Omega_p, \Omega_q) \hat{n} \cdot \nabla x(r) = \beta(\Omega_p, \Omega_q) w_b(r) \quad (8)$$

where $w_b \sim N(\mu_b, \Sigma_b)$ is a second vector of independent Gaussian variables, with non-zero mean vector μ_b and non-uniform variances. A zero boundary condition is used at the external boundary of the medium. The parameter $\beta(\Omega_p, \Omega_q)$ controls the weight of the boundary condition between regions Ω_p and Ω_q with respect to the primary differential operator without affecting the boundary condition itself. Mean values for $w_b(r)$ are computed as the difference between the means of the two adjoining regions, as determined using our parameterized solution. Variances for both $w_m(r)$ and $w_b(r)$ are determined, based on a shot noise model, assuming that the voxels within each region have a variance equal to their mean.

The above differential equation is discretized in 2D using an 8-neighborhood for the primary differential equation and a 4-neighborhood for the boundary condition. Elements of the discretized equation matrix are thus generated as:

$$W_{i,j} = \begin{cases} -\sum_{k \neq i} W_{i,k} & : i == j \\ \alpha(\Omega_p) & : x_j \in \text{Neighbors}_8(x_i) \& \\ & : \{x_j, x_i\} \in \Omega_p \\ \beta(\Omega_p, \Omega_q) & : x_j \in \text{Neighbors}_4(x_i) \& \\ & : \{x_j\} \in \Omega_p, \{x_i\} \in \Omega_q \end{cases} \quad (9)$$

This allows us to then write an equation for the image x in terms of the noise processes w_m and w_b :

$$x = W^{-1}(w_m + w_b). \quad (10)$$

This, in conjunction with $\Sigma_w = \sigma_w^2 I + \Sigma_b$, lets us express the image x statistically as $x \sim N(W^{-1}\mu_w, (W^{-1})\Sigma_w(W^{-1})^T)$. Given this prior for x , the MAP inverse solution is then:

$$\hat{x} = \arg \min_x \|b - Ax\|_2^2 + \lambda^2 \left\| \Sigma_w^{-1/2} W^T (W^{-1} \mu_w - x) \right\|_2^2 \quad (11)$$

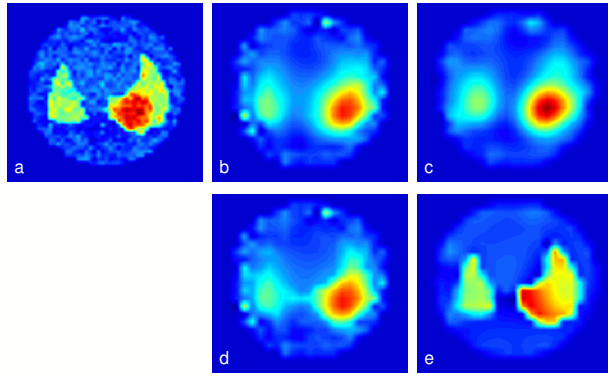


Fig. 1. Reconstructions of Simulated Fluorescence within an Artificial 2D Geometry: a) Original Fluorescence Image b-e) Reconstructions Regularized with: b) Identity Matrix c) Global Laplacian d) Varying Regularizer e) Differential Equation Based Regularization.

Figure 1d shows this method being applied to the previously described simulation experiment. For this case, we have taken $\alpha(\Omega_j) = 1 \quad \forall \Omega_j$ and $\beta(\Omega_p, \Omega_q) = 0.1 \quad \forall \Omega_p, \Omega_q$. Compared to the other two methods, this technique more accurately identifies the fluorescent inclusion, and delineates it from the background. Numerically, our solution has a 16% decrease in solution error as compared to the solution regularized with the identity, and a 9% decrease as compared to our first method. Compared to the Laplacian, a 6% decrease in error is seen.

3. CONCLUSIONS

Multimodal techniques offer the potential for significant improvements in diffusion based optical imaging. Using anatomical structure, these methods guide the formation of tomographic images to improve both spatial fidelity and quantitative accuracy. Existing methods tend to incorporate this structure in a manner which does not necessarily make optimal use of the available information. By using the data to aid in the construction of the regularization term and synthesizing differential equation based regularization operators, we hope to move towards better use of anatomical structure, and greater integration between the tomographic problem and knowledge about the underlying biological processes.

Our first step was to build a low dimensional parameterized problem from which we obtained a single value for each anatomical region. Our initial method used these values to create a regularization operator customized to the collected data and anatomical structure of the experiment. Each voxel was individually regularized based on the importance of the underlying anatomical regions. As seen in our example, this has the capacity to improve solutions by helping to localize them within the appropriate physical regions.

The parameterized solution also served as a basis for our second approach, which built a differential equation to govern the behavior of the inverse solution. A statistical prior

model for the image was implicitly defined by this equation, and was used to shape an appropriately regularized inverse problem. While the equations used here are a simple example to illustrate the potential of viewing regularization operators in this framework, they have the potential to be used in more complex situations. The final paper and talk will examine the use of these techniques in situations with incomplete or erroneous boundary information, as well as the incorporation of tissue dependant smoothing and boundary conditions, and their effects upon the resulting solutions.

We note that our framework allows for other possibilities beyond basic differential equations. If the target fluorochrome is known to behave in a specific pharmacological manner, one could use a mathematical model of that behavior to regularize the solution, while maintaining some robustness to the hypothesized segmentation. Thus, rather than penalizing based on some generalized characteristics of the solution image, the fluorescence tomography problem could be coupled both to the anatomy and underlying biochemical processes in a statistically controlled fashion.

4. REFERENCES

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